Since the phenolic hydroxyl groups of morphine compounds are generally convertible to their methyl ethers (codeine compounds), this procedure of obtaining 6β-hydroxy derivatives[1] should prove useful for the syntheses of various compounds of the isocodeine series, either by reduction of morphine derivatives and subsequent conversion to codeine derivatives, or by direct reduction of 6-keto derivatives of the codeine series. Thus, the present procedure obviates the necessity of an epimerization[10] step, and of the separation of products resulting from the hydrolysis of α-chlorocodide[11,12] or bromocodide,[12-14] which are alternate routes to obtaining isocodeine derivatives.[15]

These preliminary observations reveal that formamidinesulfinic acid reduces the 6-keto group of morphine derivatives stereoselectively to the 6β-hydroxy epimers, and that this reduction does not require the presence of the 14-hydroxy group. We also find, contrary to a recent report, that this reagent reduces carbonyl groups (at least in the morphine series) in the absence of alkoxide ions.[16] These considerations warrant further investigations to determine the scope and limitations of this potentially useful reagent.

Experimental Section

Melting points of compounds were determined on a Thomas-Hoover apparatus and are uncorrected. General experimental details were as reported earlier.[1] Experimental procedures which are similar to those mentioned earlier are not given.

17-Methyl-4,5α-epoxy-6β-hydroxy-3-methoxymorphinan (12). To a solution of **11** (75 mg, 0.25 mmol) in 20 ml of EtOH was added 10 ml of aqueous NaOH (150 mg) containing formamidinesulfinic acid (95 mg, 0.88 mmol). The resulting mixture was stirred for 1 h at 80 °C under a current of nitrogen. This reaction mixture was then stripped of EtOH and extracted with $CHCl_3$. Upon evaporation a residue of **12** was obtained in a yield of 63%. The ^1H NMR spectrum of **12** ($CDCl_3$) was superimposable with a published reference spectrum.[9]

Acknowledgment. We wish to thank Dr. Ulrich Weiss for his help and encouragement during several phases of this work. Our thanks are due to Mr. S. Theodore Bella of the Rockefeller University, New York, N.Y., for performing elemental analyses, and Mr. Charles H. Strom for proton nuclear magnetic resonance spectra. Drs. F. H. Field and D. V. Bowen of the Rockefeller University Mass Spectrometric Resource provided mass spectrometric analysis. This research was supported in part by Grant DA-00297 and SAODAP Grant DA-00458 and NIH, Division of Research Resources Grant RR-00862. Dr. Inturrisi is an Andrew W. Mellon Teacher Scientist, 1975–1976.

Registry No.—**6** HCl, 60018-68-0; **12**, 795-38-0.

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A Synthesis of (*E*)-4,6-Dimethyl-4-octen-3-one (Manicone)[1]

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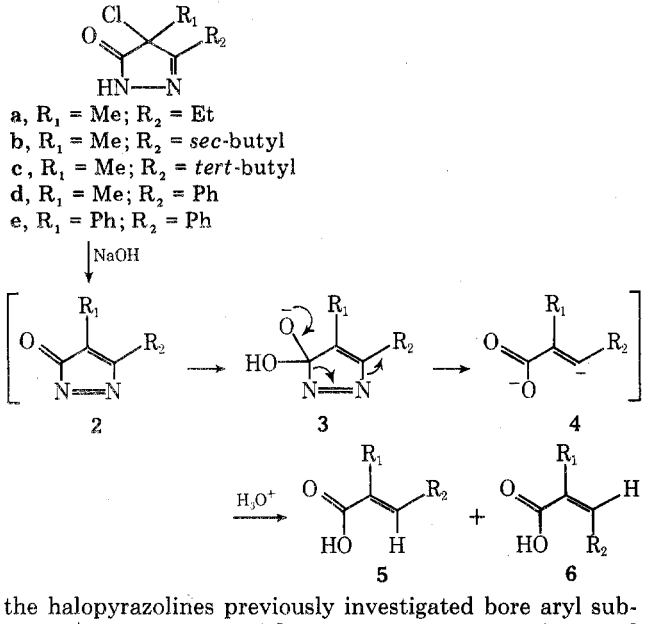
Manicone, the principal alarm pheromone of certain species of *Manica* ants, was isolated from the mandibular glands of *M. mutica* and *M. bradleyi* by Fales and co-workers and identified as (*E*)-4,6-dimethyl-4-octen-3-one (**9**).[2] The *E* stereochemistry was tentatively assigned on the basis of NMR data[2] and subsequently corroborated by a stereorational synthesis.[3] We would like to report herein a novel synthesis of manicone, the key feature of which entails the introduction of the α,β-unsaturated carbonyl moiety via the reaction of a 4-chloro-2-pyrazolin-5-one with aqueous NaOH first reported by Carpino in 1958.[4] Since the α,β-unsaturated carboxylic acids which result from this reaction can be readily converted by standard procedures to enones, the Carpino reaction was intended to serve as the fulcrum of our synthetic plan.

Carpino originally observed mixtures of both isomeric acids **5** and **6** in which the *Z* isomer **6** always predominated,[4] whereas for the manicone synthesis, the *E* isomer **5** was required. The decision to proceed in spite of these contradicting stereochemical results was based on a consideration of the proposed mechanism[4] (Scheme I). With one exception, all of

Scheme I



the halopyrazolines previously investigated bore aryl substituents at C-3 (R_2 = Ar);[5] consequently, an aryl-substituted vinyl carbanion **4** would be generated. The mixture of products observed could then be rationalized by the known relative configurational instability of aryl-substituted vinyl carbanions.[6] In the present case, however, a vinyl carbanion **4** would

Table I. Stereochemistry of the Conversion of 3,4-Dialkyl-4-chloro-2-pyrazolin-5-ones to α,β-Unsaturated Acids

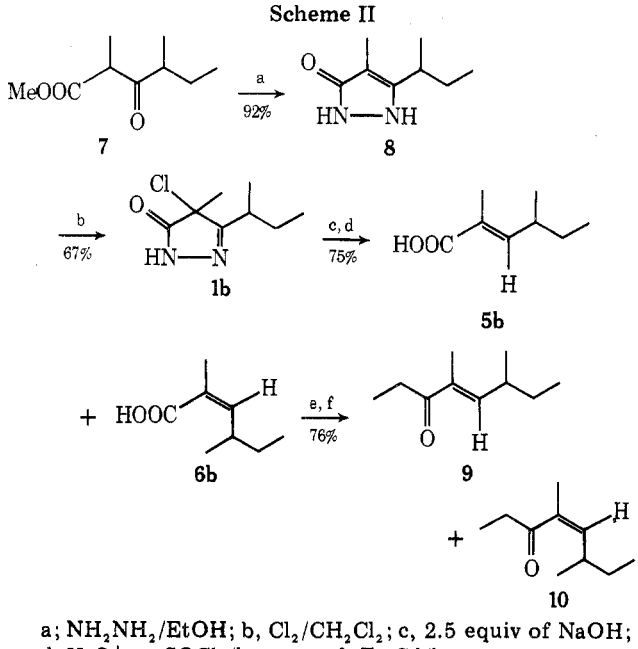
	R_1	R_2	% yield of 5 + 6[a]	Relative composition[b] 5:6
a	Me	Et	80	45:55
b	Me	*sec*-Butyl	75	45:56
c	Me	*tert*-Butyl	76	33:67
d	Me	Phenyl	69	40:60
e	Phenyl	Phenyl	55	35:65

[a] Based on products purified by distillation. [b] By integration of the vinyl proton signal in the NMR.

be generated in which R_1 = Me and R_2 = *sec*-butyl. Since alkyl-substituted carbanions invert relatively slowly,[6] the carbanion 4 (R_2 = alkyl) should protonate in an aqueous milieu much faster than invert, thereby giving the desired isomer **5** as the major product.

Manicone was prepared from β-keto ester **7** as shown in Scheme II. The mixture of carboxylic acids **5b** and **6b**, in which

Scheme II



a; NH_2NH_2/EtOH; b, Cl_2/CH_2Cl_2; c, 2.5 equiv of NaOH; d, H_3O^+; e, $SOCl_2$/benzene; f, Et_2Cd/benzene.

the *Z* isomer again predominated (**5b:6b** 44:56 by NMR analysis),[8] was converted to the corresponding acid chlorides ($SOCl_2$) which were then treated with Et_2Cd to give **9** and **10** in 76% yield for the two-step sequence. The minor ketone **9** (45% of the mixture by NMR and VPC analysis) was separated from the major *Z* isomer by preparative VPC and shown to be identical with manicone by comparison with published NMR, ir, and MS data.[2,3]

Contrary to expectation, the chloropyrazolinone **1b** failed to yield a preponderance of the *E* acid **5b**. That the stereochemical results observed for **1b** were not unique was established by investigating the reaction on the series of chloropyrazolinones **1a–e** under the conditions described for **1b** in the Experimental Section. As can be seen from the results presented in Table I, the *Z* isomer **6** was the major product in each case; thus, alkyl substitution at C-3 failed to have any pronounced effect on the stereoselectivity of the reaction.[9]

Since the overall yield for the conversion of β-keto esters to the carboxylic acids **5** and **6** was ~50% in each case, the overall process should provide a synthetically useful alternative deoxygenation procedure.

Experimental Section[10]

3-*sec*-Butyl-4-methyl-3-pyrazolin-5-one (8). A mixture of 7.00 g (40.7 mmol) of β-keto ester **7**[7] and 1.36 ml (40.7 mmol) of 95% hydrazine in 42 ml of EtOH was refluxed for 20 h. The viscous mass which was obtained after removal of solvent in vacuo was dissolved in 30 ml of CCl_4 and refrigerated. The resultant crystalline product was suction filtered and air dried to afford 5.77 g (92%) of **8** as fine, white crystals: mp 89–91 °C; ir ($CHCl_3$) 3500–2200, 1710, and 1600 cm^{-1}; NMR ($CDCl_3$) δ 11.0 (br s, 2 H), 2.6 (m, 1 H), 1.8 (s, 3 H), 1.5 (m, 2 H), 1.2 (d, 3 H), 0.8 (t, 3 H); MS *m/e* 154 (28, $M^{\cdot+}$), 139 (6), 125 (31), 119 (95), 117 (100).

4-Chloro-3-*sec*-butyl-4-methyl-2-pyrazolin-5-one (1b). A 100-ml three-neck flask fitted with a condenser, magnetic stirrer, and gas inlet tube was charged with 6.00 g (39.0 mmol) of **8** and 50 ml of CH_2Cl_2. With rapid magnetic stirring, Cl_2 gas was introduced below the surface of the suspension at ambient temperature until the mild exothermic reaction subsided with the concomitent formation of a pale orange color. Any suspended solid matter was removed by suction filtration (fritted glass, hood!) and the resultant filtrate concentrated in vacuo. The crude product was purified by short-path distillation to afford 4.92 g (67%) of **1b** as a viscous, colorless oil: bp 97–100 °C (0.1 mm); ir (CCl_4) 3460, 3230, 1755, and 1730 cm^{-1}; NMR (CCl_4) δ 10.1 (br s, 1 H), 2.5 (sextet, 1 H), 1.7 (s, 3 H) superimposed on (quintet, 2 H), 1.2 (pair of overlapping doublets, 3 H), 0.9 (t, 3 H); MS *m/e* 191 (10, $M^{\cdot+}$), 189 (30, $M^{\cdot+}$), 155 (35), 153 (100).

(*E*)- and (*Z*)-2,4-Dimethylhex-2-enoic Acid (5b, 6b). To a magnetically stirred solution of 0.5 g (12.5 mmol) of NaOH in 5 ml of water was added dropwise with ice-bath cooling 1.02 g (5.37 mmol) of **1b**. After the gas evolution had subsided, the resultant solution was extracted with ether and acidified with 3 N HCl and the products extracted into 2 × 10 ml of ether. The combined ether extracts were washed with water, dried over $MgSO_4$, and concentrated in vacuo and the crude product distilled via Kugelrohr to afford 0.63 g (75%) of a colorless oil: bp 85–87 °C (bath) (0.5 mm); ir (CCl_4) 3500–2500, 1690, and 1630 cm^{-1}. The NMR signals corresponding to the isomers **5b** and **6b** were only partially resolved in the mixture. The *E* isomer **5b** gave a doublet (with further fine splitting) for the C-3 vinyl proton at δ 6.7 whereas the signal for **6b** appeared at δ 5.8. The C-4 allylic proton appeared as multiplets centered at δ 3.2 (**6b**) and 2.3 (**5b**) whereas the C-2 methyls appeared as finely split singlets at δ 1.9 (**6b**) and 1.85 (**5b**). The overlap of the remaining signals precluded further assignments and no attempt was made to separate the mixture.

(*E*)- and (*Z*)-2,4-Dimethyl-4-octen-3-one (9, 10). A solution of 1.00 g (7.03 mmol) of a mixture of **5b, 6b,** and 1 ml of $SOCl_2$ in 5 ml of benzene was refluxed for 2 h, and then the solvent removed in vacuo. The crude product was distilled via Kugelrohr (bp 68 °C, 15 mm) to give a mixture of acid chlorides (0.94 g, 84%) as a colorless oil: ir (CCl_4) 1748, 1640 cm^{-1}. The distilled product was used in the subsequent step without further characterization.

The mixture of isomeric acid chlorides was added in one portion to 3 equiv of Et_2Cd in ~30 ml of benzene at room temperature. After refluxing for 2 h, the mixture was poured into 10 ml of 8 N HCl and 50 g of crushed ice. The aqueous layer was washed with 30 ml of ether and the combined organic layers washed with 2 × 20 ml of water. After drying over $MgSO_4$, the solvent was removed by distillation through a 15-cm Vigreux column at atmospheric pressure. The residue was distilled via Kugelrohr to give 0.70 g (76%) of the mixture of ketones **9** and **10**, bp 83 °C (bath) (20 mm). The ketones were separated by preparative VPC on a 4 ft × 0.25 in. 10% SE-30/Chromosorb P column at 130 °C to give manicone (**9**, 45%) [retention time 7.0 min; ir (CCl_4) 1680, 1610 cm^{-1}; NMR (CCl_4) δ 0.9 (t, 3 H), 1.02 (d, 3 H), 1.06 (t, 3 H), 1.4 (m, 2 H), 1.73 (d, 3 H, J = 1.4 Hz), 2.4 (m, 1 H), 2.59 (q, 2 H), 6.24 (d, 1 H, J = 10 Hz with further fine splitting)] and the *Z* isomer **10** (55%) [retention time 10.5 min; ir (CCl_4) 1715, 1635 cm^{-1}; NMR (CCl_4) δ 0.82 (t, 3 H), 0.95 (d, 3 H), 1.05 (t, 3 H), 1.3 (m, 2 H), 1.90 (d, 3 H, J = 1.4 Hz), 2.44 (q, 2 H), 2.60 (m, 1 H), 5.22 (d, 1 H, J = 10 Hz with further fine splitting)].

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Registry No.—**1a**, 60065-17-0; **1b**, 60065-18-1; **1c**, 60065-19-2; **1d**, 60065-20-5; **1e**, 13051-15-5; **5a**, 16957-70-3; **5b**, 54211-44-8; **5b** acid chloride, 54211-45-9; **5c**, 60065-21-6; **5d**, 1895-97-2; **5e**, 91-48-5; **6a**, 1617-37-4; **6b**, 60065-22-7; **6b** acid chloride, 60065-23-8; **6c**, 60065-

24-9; **6d**, 15250-29-0; **6e**, 91-47-4; **7**, 60065-25-0; **8**, 60065-26-1; **9**, 60132-36-7; **10**, 60132-37-8.

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(7) The procedure used for the preparation of **7** was derived from A. P. Krapcho, J. Diamanti, C. Cayen, and R. Bingham, "Organic Syntheses", Collect. Vol. V, Wiley, New York, N.Y., 1973, p 198: bp 102–105 °C (20 mm); ir (CCl_4) 1750, 1720 cm^{-1}; NMR (CCl_4) δ 3.7 (s, 3 H), 3.7 (q, 1 H), 2.7 (quintet, 1 H), 1.6 (m, 2 H), 1.3 (d, 3 H), 1.1 (d, 3 H), 0.9 (t, 3 H).
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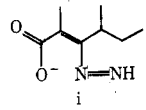
(9) An alternative to the Scheme I mechanism entails hydrolytic cleavage of **2** to the vinyl diimide i which may then undergo radical decomposition to the observed products. ESR studies have shown that vinyl radicals invert



i

rapidly at −180 °C: O. Simamura, *Top. Stereochem.*, **4**, 21 (1969). The insensitivity of the **5b:6b** ratio to substitution at C-3 lends support to the notion of a linear radical or rapid inversion of a trigonal vinyl radical relative to the rate of capture by a hydrogen atom.
(10) Infrared and NMR spectra were recorded in CCl_4 solution with Perkin-Elmer 457 and Varian HA-100 instruments, respectively. Mass spectra were obtained with a Du Pont 29-491B spectrometer.

A Convenient Synthesis of Quinones from Hydroquinone Dimethyl Ethers. Oxidative Demethylation with Ceric Ammonium Nitrate

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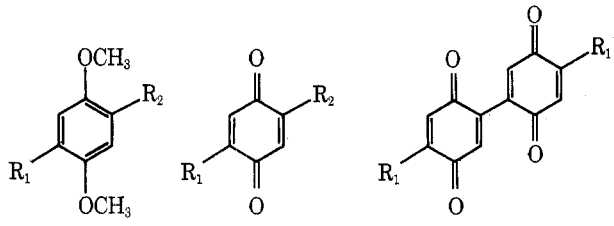
The oxidation of *p*-dimethoxybenzene derivatives to the corresponding benzoquinones has been accomplished using a variety of oxidizing agents,[1] particularly nitric acid[1] and argentic oxide.[2] Nitric acid works well for highly substituted 1,4-dimethoxybenzene derivatives, but in some instances nitration of the aromatic ring occurs in addition to or instead of demethylation. Argentic oxide appears to be quite broad in its application, but the reagent is relatively expensive and may be inconvenient for large scale preparations. Both nitric acid and argentic oxide require strongly acidic media, and acid labile functional groups may not be tolerated.

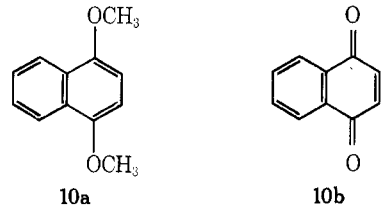
As a part of our studies on the metabolism and mechanism of action of psychotomimetic 1-phenyl-2-aminopropanes, we required a mild method for the oxidative demethylation of *p*-dimethoxybenzene derivatives. We have found that ceric ammonium nitrate [$Ce(NH_4)_2(NO_3)_6$, CAN] in aqueous acetonitrile will oxidize a variety of hydroquinone dimethyl ethers (**a**) to the corresponding quinones (**b**) often in high yield. The reaction can be carried out in the absence of strong acid, and is generally quite fast, requiring only a few minutes reaction time at room temperature. The selectivity and mildness of the reaction is illustrated by the fact that a variety of functional groups are tolerated. For example, the acid labile *tert*-butoxycarbonyl function survived the oxidation of **6a** to **6b**. Especially noteworthy is the facile conversion of the benzyl alcohol **3a** to the quinone **3b**, since CAN has been reported to oxidize benzylic alcohols to the corresponding benzaldehydes.[4]



a b c

Compd	R_1	R_2
1	H	H
2	CH_3	CH_3
3	CH_3	CH_2OH
4	CH_3	$CH{=}C(CH_3)NO_2$
5	CH_3	$CH_2CH(CH_3)NHCOCH_3$
6	CH_3	$CH_2CH(CH_3)NHCO_2C(CH_3)_3$
7	OCH_3	$CH_2CH(CH_3)NHCOC_6H_5$
8	CH_3	H
9	OCH_3	H

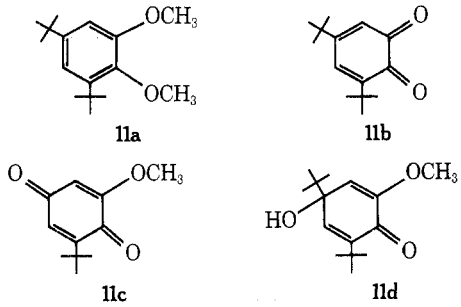
Generally, good yields of *p*-benzoquinones were obtained from 2,5-disubstituted 1,4-dimethoxybenzene derivatives. With the monosubstituted derivative 2,5-dimethoxytoluene (**8a**), however, the major product was a dimer, 4,4′-dimethylbiphenyl-2,5,2′,5′-diquinone (**8c**).[3,5] Similar results were obtained with 1,2,4-trimethoxybenzene (**9a**). In the case of the completely unsubstituted *p*-dimethoxybenzene (**1a**) a moderate (57%) yield of benzoquinone (**1b**) was obtained. Apparently, the yield was reduced by competitive dimerization, although no attempt to characterize side products was made. As an example of naphthoquinone formation, oxidation of



10a **10b**

1,4-dimethoxynaphthalene (**10a**) to naphthoquinone (**10b**) was achieved in nearly quantitative yield.

Our success in the synthesis of *p*-quinones encouraged us to attempt to extend the reaction to the synthesis of *o*-quinones. Attempted oxidation of 1,2-dimethoxybenzene to *o*-benzoquinone was unsuccessful, presumably owing to oxidative coupling reactions and/or the instability of the product. On the assumption that bulky substituents might inhibit coupling reactions and stabilize the product, we carried out the oxidation of 3,5-di-*tert*-butyl-1,2-dimethoxybenzene (**11a**). This reaction produced the desired *o*-quinone **11b**, as well as a second product, *p*-quinone **11c**, which must result from cleavage of a *tert*-butyl group from the aromatic ring. This rather remarkable transformation can be rationalized



11a **11b**

11c **11d**